

5.09 MOGAMULIZUMAB, Solution concentrate for I.V. infusion 20 mg in 5 mL, Poteligeo[®], Kyowa Kirin Australia Pty Ltd

1 Purpose of submission

- 1.1 The submission requested an Authority Required listing for mogamulizumab for the treatment of patients with relapsed or refractory cutaneous T cell lymphoma (CTCL) disease following at least one prior systemic treatment for the condition.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus vorinostat. The key components addressed by the submission are presented in Table 1. While the primary and secondary clinical claims in the submission refer to the specific CTCL subtypes for which evidence was provided (mycosis fungoides – MF and Sezary syndrome – SS) the proposed PBS listing was agnostic to disease subtype.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population ^{a,b}	CTCL including MF, SS, pcALCL and LyP and various other less common T cell lymphomas and lymphoproliferative disorders as specified by the WHO-EORTC Classification System for CTCL.
Intervention	Mogamulizumab 1.0 mg/kg IV weekly on days 1, 8, 15 and 22 of the first cycle, followed by every 2 weeks on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.
Comparator	Main: Vorinostat 400 mg orally daily, until disease progression or unacceptable toxicity. Secondary: Brentuximab 1.8 mg/kg IV every 3 weeks, for up to 16 cycles ^c
Outcomes	PFS, ORR, TTR, DOR, TTNT, OS, HRQoL and Safety
Clinical claim	Primary: In patients with MF or SS which is relapsed or refractory after at least one prior systemic therapy, mogamulizumab provides significantly and importantly superior effectiveness with different but generally non-inferior safety to the main comparator vorinostat. Secondary: In patients with MF or SS which is relapsed or refractory after at least one prior systemic therapy, mogamulizumab provides a qualitatively (but unquantifiably) different mix of efficacy and safety effects to the secondary comparator brentuximab. ^{c,d}

Source: Table 1-1, p30 of the submission.

Abbreviations: CTCL = cutaneous T cell lymphoma; DOR = duration of response; HRQoL = health related quality of life; IV = intravenous; LyP = lymphomatoid papulosis; MF = mycosis fungoides; ORR = overall response rate; OS = overall survival; pcALCL = primary cutaneous anaplastic large-cell lymphoma; PFS = progression free survival; SS = Sezary syndrome; TTNT = time to next treatment; TTR = time to response; WHO-EORTC = World Health Organization-European Organization for Research and Treatment of Cancer

^a The requested population in the submission is in the relapsed or refractory CTCL population after at least one prior systemic therapy.

^b The requested population is the same as the PBS population for vorinostat but is not restricted to those who are SCT ineligible; however, the primary clinical claim is in patients with MF or SS based on MAVORIC which is narrower than the stated population.

^c Based on the clinical evidence provided to justify the clinical claims, the mention of 'brentuximab' in the submission refers to the antibody-conjugated brentuximab vedotin.

^d The secondary clinical claim states patients with MF or SS, however in section 2 (p61 of the submission) the claim is made for patients with CTCL (with no subgroup specification).

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** No TGA documents were available.
- 2.2 The PBAC noted that mogamulizumab is not currently TGA approved. An application to register mogamulizumab was filed with the TGA under the new Comparable Overseas Regulators pathway on 18th February 2020. The outcome of the first round evaluation was not anticipated until 31 July 2020 with a decision from the TGA Delegate not expected until 7 January 2021.
- 2.3 The requested TGA indication was “for the treatment of adult patients with mycosis fungoides (MF) or Sezary syndrome (SS) who have received at least one prior systemic therapy.”
- 2.4 Mogamulizumab was approved for CTCL (without reference to subtype specification) in 2014 in Japan and for MF and SS in 2018 by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The proposed restriction for mogamulizumab on the PBS is as monotherapy, for relapsed or refractory CTCL after at least one prior systemic therapy. The submission proposed separate listings for initial and continuing therapy. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Dispensed Price Max. Qty	Manufacturer
MOGAMULIZUMAB Injection	NEW (Public) NEW (Private)	120 mg	7	Published Public: \$ 15,055.06 Private: \$ 15,304.40 Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	Kyowa Kirin Australia Pty Ltd
Available brands					
Poteligeo (mogamulizumab 20 mg/5 mL injection, 5 mL vial)					

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – delayed/non-real time assessment by Services Australia (written application lodged by mail or electronic upload) <input checked="" type="checkbox"/> Authority Required - <i>immediate/real-time assessment by Services Australia (Telephone/Online)</i>
Condition: Cutaneous T-cell lymphoma
Indication: Cutaneous T-cell lymphoma

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Treatment Phase: Initial treatment
Clinical criteria:
<i>Patient must have a diagnosis of mycosis fungoides; or</i>
<i>Patient must have a diagnosis of Sezary syndrome</i>
AND
Clinical criteria:
<i>Patient must have received at least one prior systemic therapy treatment for this condition.</i>
AND
Clinical criteria:
<i>Patient must have relapsed or refractory disease following prior systemic therapy for this condition. The condition must be relapsed or refractory</i>
AND
Clinical criteria:
<i>The treatment must not exceed a total of 8 doses under this restriction.</i>
AND
Clinical criteria:
<i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition.</i>
Prescribing Instructions:
<i>Applications for authorisation of initial treatment must be in writing and must include:</i>
<i>(a) a completed authority prescription form; and</i>
<i>(b) a completed cutaneous T-cell lymphoma (CTCL) initial PBS Authority Application – Supporting Information Form</i>
Administrative Advice:
<i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>
<i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</i>
<i>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</i>
<i>Or mailed to:</i>
<i>Services Australia</i>
<i>Complex Drugs</i>
<i>Reply Paid 9826</i>
<i>HOBART TAS 7001</i>
Administrative Advice:
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Dispensed Price Max. Qty	Manufacturer
MOGAMULIZUMAB Injection	NEW (Public) NEW (Private)	120 mg	5	Published Public: \$ 15,055.06 Private: \$ 15,304.40 Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	Kyowa Kirin Australia Pty Ltd
Available brands					
Poteligeo (mogamulizumab 20 mg/5 mL injection, 5 mL vial)					

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (Telephone/Online)
Condition: Cutaneous T-cell lymphoma
Indication: Cutaneous T-cell lymphoma
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: The treatment must be the sole PBS-subsidised systemic <i>anti-cancer</i> therapy for this condition.
Administrative Advice: [if a telephone/online Initial treatment Authority approval is recommended by PBAC] Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
Administrative Advice: [if a written-only Initial treatment Authority listing is recommended by PBAC] Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

- 3.2 A special pricing arrangement based on a [REDACTED] % rebate on the published approved ex-manufacturer price (AEMP) was proposed, resulting in a published AEMP of \$ [REDACTED] and an effective AEMP of \$ [REDACTED] for a 1 x 20 mg vial. The effective dispensed price per maximum amount (DPMA) was calculated based on the effective AEMP (this was \$ [REDACTED] for the private sector).
- 3.3 The requested TGA indication is specific to the MF and SS subtypes of CTCL, based on the pivotal clinical trial, MAVORIC, which limited recruitment to patients with either MF or SS. However, the submission requested that mogamulizumab be made available on the PBS for the treatment of CTCL irrespective of subtype and disease stage. The submission justified this approach based on the CCR4-mediated mechanism of action

of mogamulizumab and the almost universal overexpression of these receptors to some extent in all CTCL subtypes. However, the submission did not present clinical evidence of the extent of CCR4 expression in CTCL subtypes or the use of mogamulizumab in CTCL subtypes other than MF or SS. The Pre-Sub-Committee Response (PSCR) stated there are only limited and heterogeneous data available in relation to this issue, however these data suggest CCR4 is typically overexpressed by a significant majority of patients with CTCL subtypes other than MF or SS.

- 3.4 In considering the November 2018 application to list brentuximab vedotin (hereafter referred to as brentuximab), the PBAC noted that the lymphomatoid papulosis (LyP) subtype of CTCL is not consistently defined as a cancer, can resolve without treatment and does not affect life-expectancy. Therefore, the PBAC recommended that patients with the LyP CTCL subtype be excluded from PBS subsidised access to brentuximab (paragraph 5.10, brentuximab vedotin Public Summary Document (PSD), November 2018 PBAC meeting). The PSCR noted that the restriction for the main comparator, vorinostat, permits use in any CTCL subtype, which would generally be interpreted to include LyP.
- 3.5 The PBAC noted the clinical evidence from MAVORIC was limited to patients with MF or SS. The PBAC also noted the differences in the 5 year disease-specific survival times across CTCL subtypes.¹ The PBAC considered it to be appropriate to exclude PBS subsidised access to mogamulizumab for CTCL subtypes such as LyP and pcALCL where $\geq 95\%$ of patients were alive at 5 years.
- 3.6 Consistent with brentuximab, the proposed PBS listing is not restricted to patients ineligible for stem cell transplantation (SCT); the listing for vorinostat is restricted to patients ineligible for SCT. The international treatment guidelines for CTCL do not state the timing of allogeneic SCT with respect to the numerous biological agents that are becoming available (see the British Association of Dermatologists/United Kingdom Cutaneous Lymphoma Group guidelines; Gilson 2019). While the submission did not propose the specific exclusion of SCT eligible patients, there are safety concerns with undergoing an allogeneic transplant following mogamulizumab treatment, such as increased risk of severe graft versus host disease. Moreover, the economic evaluation presented in Section 3 was based on a survival analysis which excluded patients who subsequently had an SCT.
- 3.7 The submission requested that the definition of prior systemic therapy in the PBS listing not be limited to chemotherapy (as currently applies to the vorinostat listing). This is consistent with the clinical evidence as a high proportion of patients enrolled in the MAVORIC trial had received prior CTCL treatment with conventional

¹ Willemze RL. et.al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood* 2019;133:1703-1714.

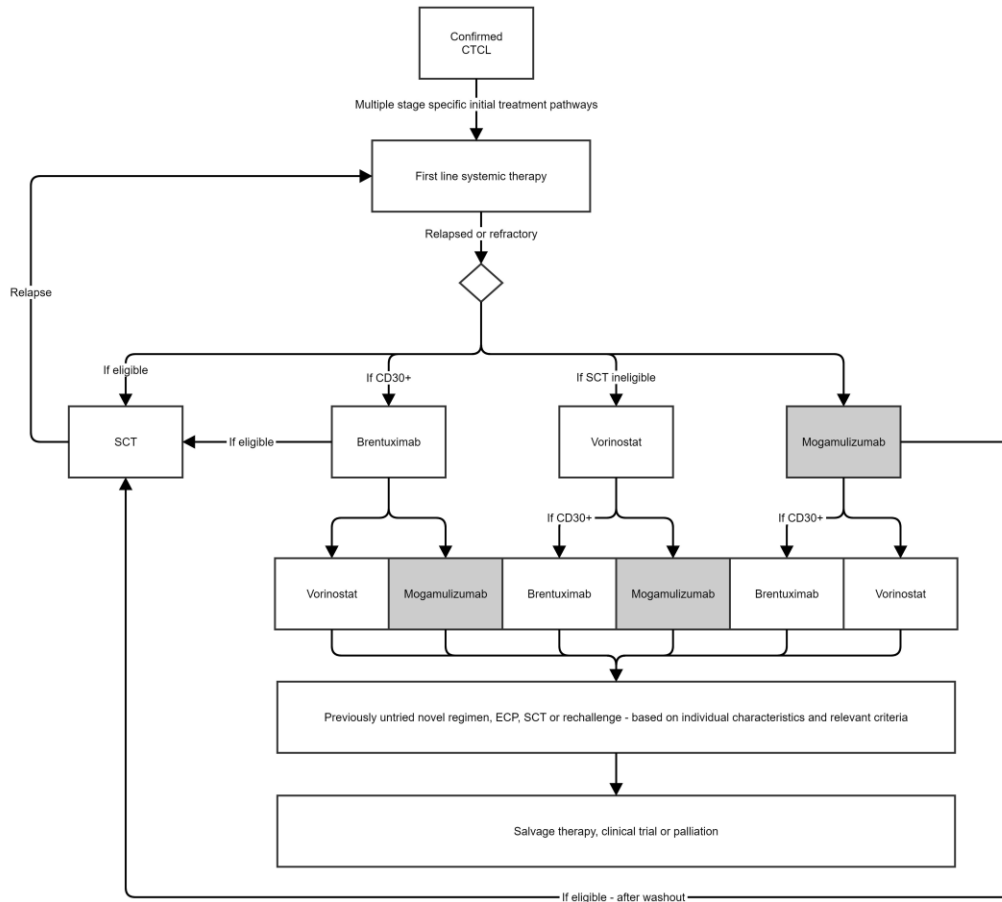
chemotherapy as well as other therapies such as bexarotene and interferon (Kim, 2018).

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Lymphoma is a haematological cancer of the lymphocytes. CTCL is a rare subtype of Non-Hodgkin lymphoma (2-3% of cases) that presents with skin manifestation at diagnosis and eventually involves the lymph nodes, blood and internal organs (p1, Vorinostat, PSD, March 2011 PBAC meeting). The two most common forms of CTCL are MF or SS which comprise approximately two-thirds of CTCL cases, the remainder are various CD30+ primary cutaneous lymphoproliferative disorders, most notably primary cutaneous anaplastic large cell lymphoma (pcALCL) and LyP.
- 4.2 Mogamulizumab is a defucosylated, humanised IgG1 kappa immunoglobulin that selectively binds to C-C chemokine receptor type 4 (CCR4), a G-protein-coupled that is involved in the trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells. CCR4 is inherently expressed on the surface of certain T cell malignancies, such as MF and SS.
- 4.3 The submission stated that the Australian lymphoma guideline was updated in 2009, and was no longer reflective of current clinical practice. Hence, the algorithm presented in the submission was said to be a simplified partial Australian treatment algorithm which reflects current real-world practice. The submission's proposed place in therapy for mogamulizumab in CTCL is presented in Figure 1.

Figure 1: Proposed simplified partial Australian treatment algorithm



Source: Figure 1-10, p48 of the submission.

Abbreviations: CTCL = cutaneous T cell lymphoma; ECP = extracorporeal photopheresis; SCT = stem cell transplantation

4.4 The ESC considered that relapsed or refractory CTCL was a relatively rare lymphoma with high symptom burden for which there were currently limited treatment options. The PBAC noted that the Medical Services Advisory Committee (MSAC) recently supported public funding through the Medicare Benefits Schedule for the use of extracorporeal photopheresis for patients with erythrodermic (stage T4 M0) CTCL who are refractory to one or more systemic therapies.²

For more detail on PBAC’s view, see section 7 PBAC outcome.

² Medical Services Advisory Committee (MSAC). Application No. 1420.1 – Extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma. MSAC Public Summary Document. April 2020 [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/91FE1B55FB6A77E9CA2584EE008194C0/\\$File/1420.1%20Final%20PSD_Apr2020_redacted.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/91FE1B55FB6A77E9CA2584EE008194C0/$File/1420.1%20Final%20PSD_Apr2020_redacted.pdf)

5 Comparator

- 5.1 The submission nominated vorinostat as the main comparator. The ESC considered the justification and choice of vorinostat as the main comparator was reasonable.
- 5.2 The submission nominated brentuximab as a secondary comparator. Brentuximab is PBS listed for a subgroup of CTCL patients with CD30+ MF, SS or pcALCL who have relapsed or refractory disease with prior systemic treatment. The submission stated that this population partially overlaps with the proposed mogamulizumab population, in that any patient eligible for brentuximab would also be able to receive mogamulizumab, but only a subgroup of CD30+ patients would be eligible to receive brentuximab. The ESC considered the nomination of brentuximab as a secondary comparator was reasonable.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the high symptom burden often faced by patients with relapsed or refractory CTCL. Comments from the Leukaemia Foundation, Rare Cancers Australia and Lymphoma Australia highlighted the need for new treatment options in the management of this rare cancer.

Clinical trials

- 6.3 The submission was based predominantly on one head-to-head phase 3, open-label, randomised clinical trial (RCT), MAVORIC (N = 372) comparing mogamulizumab with vorinostat in patients with MF or SS CTCL subtypes following at least one prior systemic therapy. For the secondary comparator, brentuximab, the submission presented a naïve comparison between the MAVORIC and ALCANZA (N = 131) trials. ALCANZA was a phase 3, open-label, RCT comparing brentuximab and physician choice of bexarotene or methotrexate for previously treated patients with CD30+ MF or pcALCL subtypes of CTCL.
- 6.4 Six supplementary non-randomised trials were also presented as supportive evidence:
- Two mogamulizumab trials: KW-0761-001 (N = 41) a phase I/II trial in previously treated peripheral T cell lymphoma or CTCL; and KW-0761-004 (N = 38), a late phase II trial in CCR4-positive peripheral T/NK-cell lymphoma.
 - Two vorinostat trials: Study P001 (N = 74), a phase IIb trial in advanced CTCL; and Study P005 (N = 33) a phase II trial in refractory CTCL.

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- Two brentuximab trials: Duvic 2015 (N = 48), a phase II trial in CD30+ CTCL and LyP; and Kim 2015 (N = 32), a phase II investigator-initiated trial in MF and SS with CD30 expression.

6.5 Details of the two RCTs and six non-randomised trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication Citation
Mogamulizumab and vorinostat randomised trial		
MAVORIC KW-0761-010 NCT01728805 ^a	Open-label, Multi-center, Randomised Study of Anti-CCR4 Monoclonal Antibody KW-0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-cell Lymphoma (CTCL)	August 2017
	Kim Y, Bagot M, Pinter-Brown L, al e. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial.	<i>Lancet Oncol.</i> 2018.
Mogamulizumab non-randomised trials		
KW-0761-001 NCT00888927	Open-label, Multi-center, Dose Escalation Phase 1/2 Study of Anti-CCR4 Monoclonal Antibody KW-0761 as Monotherapy in Subjects with Previously Treated Peripheral T-cell Lymphoma or Cutaneous T-cell Lymphoma	March 2016
	Duvic M, Pinter-Brown L, Foss F, al e. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma.	<i>Blood.</i> 2015;125(12):1883-9.
KW-0761-004 NCT01192984	A Late Phase II Study of KW-0761 in Subjects with CCR4-Positive Peripheral T/NK-Cell Lymphoma	March 2014
	Ogura M, Ishida T, Hatake K, al e. Multicenter Phase II Study of Mogamulizumab (KW-0761), a Defucosylated Anti-CC Chemokine Receptor 4 Antibody, in Patients With Relapsed Peripheral T-Cell Lymphoma and Cutaneous T-Cell Lymphoma.	<i>Journal of Clinical Oncology.</i> 2014;32:1157-63.
Vorinostat non-randomised trials		
Study P001 NCT00091559	Phase IIb Multicenter Clinical Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA) in Advanced Cutaneous T-cell Lymphoma	March 2006
	Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma.	<i>J Clin Oncol.</i> 2007;25(21):3109-15.
	Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma.	<i>Clin Lymphoma Myeloma.</i> 2009; 9(6):412-6
Study P005	Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL).	<i>Blood.</i> 2007;109(1):31-9.
Brentuximab randomised trial		
ALCANZA NCT01578499	A Randomized, Open-Label, Phase 3 Trial of Brentuximab Vedotin(SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30+ Cutaneous T-Cell Lymphoma	July 2018
	Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, et al. Brentuximab vedotin or physician's choice in CD30+ cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. <i>Lancet.</i>	<i>Lancet</i> 2017; 390(10094): 555-66
Brentuximab non-randomised trials		
Duvic 2015	Phase II Trial of Brentuximab Vedotin (SGN-35) at Dose of 1.8 mg/kg IV	July, 2019

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Trial ID	Protocol title/Publication title	Publication Citation
NCT01352520	Every 3 Weeks in Patients With CD30+ Lymphoproliferative Disorders (Cutaneous Anaplastic Large T-cell Lymphoma (ALCL), Mycosis Fungoides, and Extensive Lymphomatoid Papulosis (LyP))	
	Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a Phase II Trial of Brentuximab Vedotin for CD30+ Cutaneous T-Cell Lymphoma and Lymphomatoid Papulosis.	<i>J Clin Oncol.</i> 2015;33(32):3759-65.
	Lewis DJ, Talpur R, Huen AO, Tetzlaff MT, Duvic M. Brentuximab Vedotin for Patients With Refractory Lymphomatoid Papulosis: An Analysis of Phase 2 Results.	<i>JAMA Dermatol.</i> 2017;153(12):1302-6.
Kim 2015 NCT01396070	Exploratory Pilot Study of Brentuximab Vedotin (SGN-35) in Patients With Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level	May 2016
	Kim Y, Tavallae M, Sundram U, al. e. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sezary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project.	<i>J Clin Oncol.</i> 2015;33(32):3750-8

Source: Table 2-1 of the submission, Consolidated reference library provided by the submission in Endnote.

^a The submission presented a Supplementary Report: Quality of Life Analysis in Subjects with Cutaneous T-Cell Lymphoma Treated with Anti-CCR4 Monoclonal Antibody KW-0761 (Mogamulizumab) Versus Vorinostat; (1 August 2017). However, this is not a published paper, and it is uncertain as to whether this information is publicly available.

6.6 The key features of the included evidence are summarised in Table 3. Overall the presentation of the evidence from the non-randomised trials did not advance the evidence beyond that presented from the direct RCT (MAVORIC) for the primary comparison or the naïve comparison (MAVORIC vs ALCANZA) in that it did not present information on CTCL subtypes other than MF or SS (for mogamulizumab) and was not sufficiently comparable with the evidence from the RCTs to better inform those comparisons. Accordingly, no further discussion of the non-randomised trials is presented.

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Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias ^g	Patient population	Outcome(s)	Use in modelled evaluation
Mogamulizumab vs vorinostat						
MAVORIC	372	R, OL 17 months	High ^h	MF or SS ≥ 1 prior systemic therapy	PFS, ORR, DOR, TTF, TTR, HRQoL, AEs, TTNT ^a	TTF, PFS, TTNT, OS
KW-0761-001 (mogamulizumab)	41 ^b	MC, OL, two- part ^c	High	MF or SS ≥ 1 prior systemic therapy	ORR, DOR, TTP, TTR, PFS	Not used
KW-0761-004 (mogamulizumab)	37 ^d	Single-arm, MC, OL ^c	High	CCR4+ PTCL or CTCL Relapsed after last systemic chemotherapy	BOR, PFS, OS	Not used
Study P001 (vorinostat)	74	Single-arm, MC, OL 14.7 months ^e	High	MF or SS ≥ 2 prior therapies	ORR by mSWAT, TTR, TTP, DOR, pruritus relief, AEs	Not used
study P005 (vorinostat)	33	OL 40 months ^e	High	CTCL Refractory or intolerant to tx	ORR, TTR, TTP, DOR, pruritus relief, AEs	Not used
Mogamulizumab vs brentuximab						
MAVORIC (mogamulizumab)	372	R, OL 17 months	High ^h	MF or SS ≥ 1 prior systemic therapy	PFS, ORR, DOR, TTF, TTR, HRQoL, AEs, TTNT ^a	TTF, PFS, TTNT, OS
ALCANZA (brentuximab)	131	R, OL 22.9 months	High ⁱ	CD30+ MF or pcALCL ≥ 1 prior systemic therapy	ORR4, ORR, CR, PR, PFS, mSWAT, DOR, EFS, HRQoL AEs	Not used
Duvic 2015 (brentuximab)	48	Single-arm, OL 27 months	High	CD30+ MF, pcALCL or LyP ≥ 1 prior therapy ^f	ORR, CR, PR, PFS, mSWAT, AEs	Not used
Kim 2015 (brentuximab)	32	Single-arm, MC, OL 71.7 weeks	High	MF or SS ≥ 1 prior systemic therapy	ORR, CR, PR, mSWAT, PFS, AEs	Not used

Source: Developed during the evaluation; Table 2-2, 2-7 (pp64,75 of the submission); pp95,99 of the submission; Table 3 (p10, Brentuximab PSD, July 2018 PBAC meeting); Olsen 2007; Duvic 2005; Duvic 2015; Kim 2015.

Abbreviations: AEs = adverse events; CCR4 = chemokine receptor 4; CR = complete response; CTCL = cutaneous T cell lymphoma; BOR = best overall response; DOR = duration of response; EFS = event free survival; HRQoL = health-related quality of life; LyP = Lymphomatoid Papulosis; MC = multi-centre; MF = mycosis fungoides; mSWAT = modified Severity Weighted Assessment Tool; N = total participants in group; OL = open label; ORR = overall response rate; ORR4 = objective global response lasting at least four months; OS = overall survival; pcALCL = primary cutaneous anaplastic large cell lymphoma; PFS = progression-free survival; PR = partial response; PTCL = peripheral T cell lymphoma; R = randomised; SS = Sezary syndrome; TTF = time to treatment failure; TTNT = time to next treatment; TTP = time to progression; TTR = time to response

^a TTNT was a post-hoc analysis.

^b 41 patients with histologically confirmed CTCL were enrolled. The study permitted inclusion of CTCL or PTCL however only one patient with PTCL was recruited. This patient was excluded from efficacy analysis to maintain a homogenous study population.

^c The median duration of follow-up was not presented in the study results.

^d Of the 37 patients 8 patients (21.6%) had CTCL and thus reflected the proposed PBS criteria; 29 (78.4%) of patients had PTCL

^e This could not be verified from the information provided in the submission but references from Table 3 (p10, Brentuximab PSD, July 2018 PBAC meeting)

^f At least one prior systemic therapy was required for MF or pcALCL, for LyP more than 10 lesions, scarring or active lesions on the face, hands or feet requiring systemic treatment were required.

^g Risk of bias for the RCTs and the six non-randomised trials were assessed using different systems. Cochrane for MAVORIC and ALCANZA and ROBINS 1 for the non-randomised studies. Due to a lack of available information for the non-randomised trials, several domains of the risk for bias criteria were classified as "Could not be assessed".

^h The risk of bias for MAVORIC is considered to be high based on the open-label nature of the trial; primary efficacy (PFS) as determined by the investigator which included the assessment of skin response which is potentially subjective in nature; and the inclusion of a one-way crossover design in which patients with either progressive disease or vorinostat intolerance were permitted to receive mogamulizumab.

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ⁱ The risk of bias for ALCANZA is considered to be high based on physicians choice of therapy (methotrexate or bexarotene) for the comparator arm; the open-label nature of the trial; and the investigator assessed skin response analysis which formed part of the independent review efficacy analysis.

- 6.7 MAVORIC recruited patients with stage IB-IV MF or SS. The study population in MAVORIC was narrower than the proposed PBS listing for mogamulizumab given that it was limited to patients with the MF or SS subtypes of CTCL.
- 6.8 Within MAVORIC there was an imbalance in the median time since initial diagnosis, which was slightly longer for the mogamulizumab arm (41.0 months; range 1.2 - 362.3 months) compared to the vorinostat arm (35.4 months; range 1.0 – 306.4 months). The median number of prior systemic therapies was three for both arms. 56.5% of patients in the mogamulizumab arm compared to 58.6% of patients in the vorinostat arm had advanced-stage MF or SS (stage \geq IIB).
- 6.9 MAVORIC allowed patients with either progressive disease (PD) or those who were unable to tolerate vorinostat to crossover to treatment with mogamulizumab. Crossover was permitted from vorinostat to mogamulizumab to encourage enrolment and minimise drop out in countries, such as Australia, where vorinostat was already available and therefore patients did not need to be enrolled in the trial to receive treatment. Inclusion of crossover may have influenced investigator assessment of disease progression (in particular as it relates to skin response, where analysis may be subjective in nature) and patient assessments of tolerance. 136 (73.1%) patients in the vorinostat arm crossed over to receive mogamulizumab; 109 (58.6%) after PD and 27 (14.5%) due to vorinostat intolerance.
- 6.10 The PSCR considered the risk of bias in MAVORIC to be moderate rather than high. The PSCR argued this was justified based on the criteria for crossover eligibility and the comparison of the progression free survival (PFS) data for the investigator (the primary endpoint) and independent review (IR) assessment. The ESC considered that as the IR assessment relied on the investigator assessment of modified Severity Weighted Assessment Tool (mSWAT) which is potentially subjective in nature, therefore, the risk of bias in MAVORIC was high. The ESC noted the PBAC had previously considered that the overall risk of bias in MAVORIC was high (paragraph 6.7, Table 3, Brentuximab PSD, July 2018 PBAC Meeting).
- 6.11 In addition, the PSCR argued the open label design of MAVORIC reflected the different method of administration and predicted side effect profiles of the respective therapies, which would have made blinding very difficult. The ESC acknowledged that it would be difficult to achieve blinding when mogamulizumab is administered intravenously and vorinostat is administered orally.
- 6.12 Patients in ALCANZA had the MF or pcALCL subtypes of CTCL with histological confirmation of CD30+ disease. Therefore, the study population in ALCANZA was narrower than the proposed PBS listing for mogamulizumab, which is agnostic to CTCL subtype and CD30 expression. Baseline patient demographics were similar between the two arms of ALCANZA. There was an imbalance in the median time since initial diagnosis between the two arms, being longer in the brentuximab arm (42.2 months)

compared to physician’s choice of methotrexate or bexarotene (PC:MTX/BEX; 37.0 months). The number of prior systemic therapies was two for both arms.

Comparative effectiveness

Mogamulizumab vs vorinostat

- 6.13 At the time of the primary analysis, the median duration of follow-up for all patients in MAVORIC was 17.0 months. 27 (14.5%) patients assigned to mogamulizumab and ten (5.4%) patients assigned to vorinostat remained on treatment. Additionally, 31 (22.8%) of the 136 patients originally assigned to vorinostat who crossed over to mogamulizumab remained on treatment. The PBAC noted that at the data cut-off the median number of cycles initiated during the randomised treatment period was 6.0 in the mogamulizumab group and 3.0 in the vorinostat group.
- 6.14 A global composite response score (GCRS; Olsen, 2011), based on response (complete and partial) in each compartment (skin, blood, lymph nodes and viscera), was used for the primary endpoint of PFS and secondary endpoint of overall response rate (ORR). Assessment of disease in each compartment was analysed based on: skin response determined using mSWAT; blood response determined by flow cytometry; and evaluation of tumour burden in lymph nodes and viscera assessed by computed tomography (CT).
- 6.15 A summary of the PFS results for MAVORIC are presented in Table 4, and the Kaplan-Meier (KM) plot for investigator assessed PFS is shown in Figure 2.
- 6.16 Median PFS as assessed by the investigator was longer in the mogamulizumab arm (7.7 months) compared to vorinostat (3.1 months); the hazard ratio (HR) of 0.53 was statistically significant ($p < 0.0001$). The one-way crossover design in MAVORIC could have biased results against vorinostat as eligibility for crossing over to mogamulizumab was either PD or intolerance to vorinostat. There were slight discrepancies between investigator and IR assessment of PFS; median PFS for mogamulizumab was one month lower in the IR assessment and was 0.7 months longer for vorinostat. The HR for IR assessed PFS was also higher at 0.64 but remained statistically significant ($p < 0.0007$). Discrepancies between investigator and IR assessed PFS may arise due to the subjective nature of some of the outcomes’ assessment informing PFS including lesion progression based on assessment of photographic evidence and mSWAT analysis. The ESC noted that a statistically significant difference in favour of mogamulizumab was reported for both investigator and IR assessed PFS.

Table 4: Results of progression free survival in MAVORIC (ITT)

	Mogamulizumab (N = 186)		Vorinostat (N = 186)		Difference in median ^a	Log rank P value	HR (95% CI)
	Progressed (n, %)	Median months (95% CI)	Progressed (n, %)	Median months (95% CI)			
Investigator Assessed (Primary endpoint)	110 (59.1)	7.7 (5.7, 10.3)	131 (70.4)	3.1 (2.9, 4.1)	4.6	<0.0001	0.53 (0.41, 0.69)

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	Mogamulizumab (N = 186)		Vorinostat (N = 186)		Difference in median ^a	Log rank P value	HR (95% CI)
	Progressed (n, %)	Median months (95% CI)	Progressed (n, %)	Median months (95% CI)			
Independent Review (Secondary endpoint)	110 (59.1)	6.7 (5.6, 9.4)	122 (65.6)	3.8 (3.0, 4.7)	2.9	<0.0007	0.64 (0.49, 0.84)

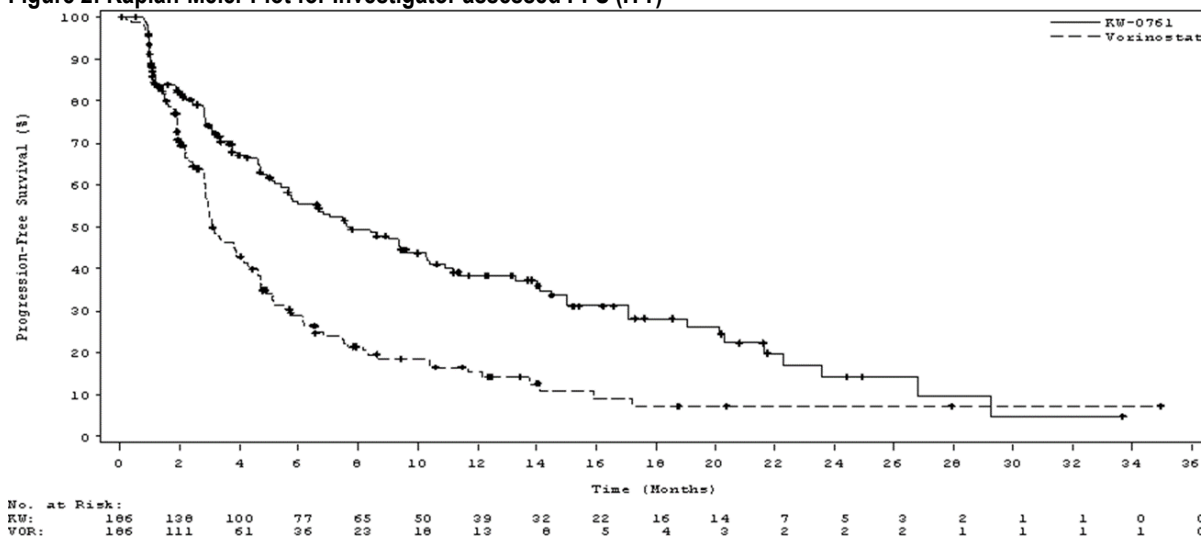
Source: Table 2-28 (p109 of the submission), Table 11.4.1-3 p130 MAVORIC CSR.

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = number of participants with event; N = total participants in group; PFS = progression free survival.

Bold indicates statistically significant difference.

^a Calculated during the evaluation

Figure 2: Kaplan-Meier Plot for Investigator assessed PFS (ITT)



Source: Figure 2-12 (p110 of the submission)

6.17 The ESC noted a high number of patients in both arms were censored from the primary analysis for PFS (40.9% of mogamulizumab arm and 29.6% of vorinostat arm). The majority of censored observations were due to patients who discontinued randomised treatment without documented PD. Of these patients, the proportion of patients censored due to discontinuation for AE or intolerance was lower for the mogamulizumab arm than for the vorinostat arm (19.7% vs 47.3%), while the proportion censored due to discontinuation for clinical PD was slightly higher in the mogamulizumab arm (25.0% vs 18.2%). Clinical progression was defined as subjects with PD who did not meet criteria for PD based on CTCL response criteria. High rates of censoring are likely to affect PFS estimates. However, the magnitude of this effect is unknown.

6.18 The ESC noted that within the crossover population, the median PFS (calculated from the first dose of mogamulizumab) was 8.9 months (95% CI: 5.4, 14.8). This is longer than the observed PFS in either the mogamulizumab or vorinostat arms (7.7 months; 95%CI 5.7, 10.3 vs 3.1 months; 95%CI 2.9, 4.1). It is unclear whether this was due to the additive therapeutic effect of the vorinostat-mogamulizumab sequence or to

underlying patient/disease characteristics (that may have influenced patient response); the submission did not address potential differences observed in outcomes due to treatment sequencing.

- 6.19 Results for investigator assessed and confirmed ORR based on IR including stratification by CTCL subtypes are presented in Table 5. The PBAC noted that both investigator assessed and IR ORR were statistically significant in favour of mogamulizumab. Subgroup analysis by CTCL subtype showed a numerically greater risk difference for patients with SS than with MF, but both subtypes presented statistically significantly higher ORR for mogamulizumab. However, the PBAC again noted that the vorinostat ORR in the MAVORIC trial was substantially lower than those reported in the P001 and P005 studies which formed the basis of the March 2017 recommendation for vorinostat listing on the PBS (paragraph 6.12, brentuximab PSD, July 2018 PBAC Meeting). The PBAC recalled that it had considered the differences in ORR were not fully explained by the use of the “more stringent” 2011 ISCL/EORTC guideline definitions of response in the MAVORIC trial and the Committee considered that the relatively short duration of vorinostat treatment (see paragraph 6.13) may also be a contributing factor.

Table 5: Results of overall response rate in MAVORIC (ITT; MF and SS subgroups)

Analysis group	n/N (%)		Risk difference (95% CI)	p-value
	Mogamulizumab	Vorinostat		
All Subjects (ITT)				
Investigator assessed ORR ^a (95% CI)	52/186 (28.0) (21.6, 35.0)	9/186 (4.8) (2.2, 9.0)	23.1 (12.8, 33.1)	<0.0001
Independent review ORR ^a (95% CI)	43/186 (23.1) (17.3, 29.8)	7/186 (3.8) (1.5, 7.6)	19.4 (9.0, 29.4)	<0.0001
MF subtype				
Investigator assessed ORR ^a (95% CI)	22/105 (21.0) (13.6, 30.0)	7/99 (7.1) (2.9, 14.0)	13.9 (0.1, 27.4)	0.0042
SS subtype				
Investigator assessed ORR ^a (95% CI)	30/81 (37.0) (26.6, 48.5)	2/87 (2.3) (0.3, 8.1)	34.7 (19.9, 48.4)	<0.0001

Source: Table 2-32 (p114 of the submission), Table 11.4.2-2 p138 MAVORIC CSR.

Abbreviations: CI = confidence interval; CR = complete response; ITT = intent to treat; n = number of participants with event; MF = mycosis fungoides; N = total participants in group; NR = not reported; ORR= overall response rate; PR = partial response

Bold indicates statistically significant difference.

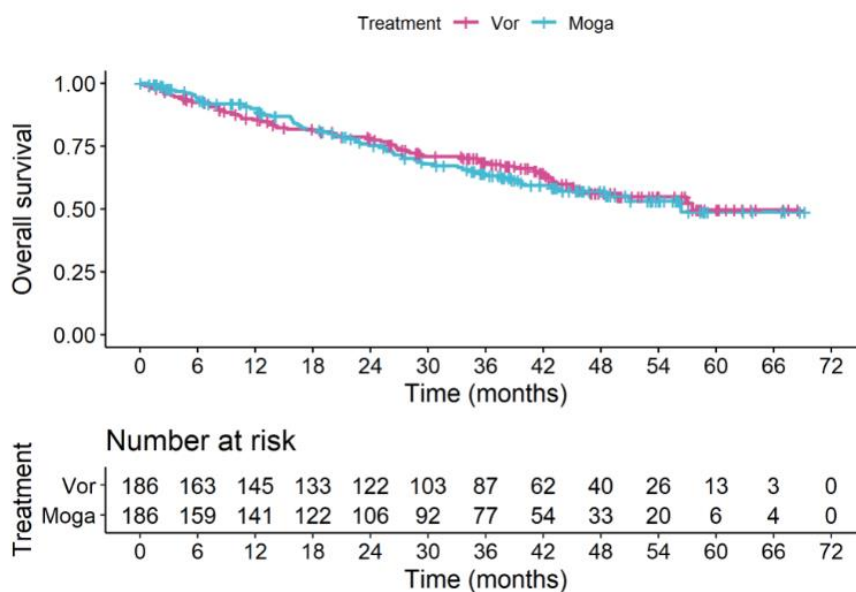
^a ORR includes patients with confirmed CR + PR

- 6.20 Best overall global response was higher in the mogamulizumab arm compared to vorinostat (35% vs 6%) and double the proportion of patients in the mogamulizumab arm compared with the vorinostat arm had at least a 50% improvement in skin response (44% mogamulizumab vs 22% vorinostat; p8 Kim et al, 2018). Of the 136 crossover patients, investigator assessed response to mogamulizumab was observed in 41 (30.1%; 95%CI 22.6, 38.6) patients, which was similar to that in the randomised mogamulizumab arm of the trial (28%; 95%CI 21.6, 35.0).
- 6.21 The median time to response (TTR) was shorter in the mogamulizumab arm at 3.3 months (IQR 2.0 – 6.4), compared to vorinostat at 5.1 months (IQR 2.9 – 8.5; p8 Kim,

2018). The median investigator assessed duration of response (DOR) for confirmed responders (as per TTR) was 14.1 months (95% CI: 9.43, 19.17) for mogamulizumab and 9.1 months (95%CI 4.7, not estimable) for vorinostat. However, this comparison is confounded by the low number of responders for vorinostat (n=9; and 5 of these patients were censored for DOR).

- 6.22 Health related quality of life (HRQoL) was measured using the Skindex-29, FACT-G and EQ-5D-3L; and evaluation of pruritus was assessed using the ItchyQoL and the Pruritus Likert Scale. Mogamulizumab treated patients had a greater improvement in their patient reported outcome (PRO) at the 6-month assessment than those in the vorinostat arm, which was statistically significant. The PBAC considered that missing data, including missing data by design, may limit the conclusions that can be drawn regarding HRQoL.
- 6.23 Exploratory outcomes for MAVORIC included time to treatment failure (TTF), and overall survival (OS). The number of patients with treatment failure was higher in the vorinostat arm compared to the mogamulizumab arm (176 patients; 94.6% vs 157 patients; 84.4%). The median TTF was longer in the mogamulizumab arm compared to vorinostat (5.8 vs 2.9 months; HR 0.58; 95% CI: 0.47, 0.72, $p < 0.0001$; p151, MAVORIC CSR).
- 6.24 At the primary analysis (31st December, 2016), median OS was not reached in the mogamulizumab arm compared to 43.9 months (95%CI 43.6, NR) for vorinostat (HR 0.93; 95%CI 0.61, 1.43; $p = 0.94$). An updated analysis of OS (2nd March 2019) was also presented in the submission and did not show any separation in the OS curves (see Figure 3). The updated KM analysis was consistent with the OS results from the primary analysis.

Figure 3 Kaplan-Meier analysis of OS (ITT; 2nd March 2019 analysis)



Source: Figure 2-32 (p147 of the submission).

- 6.25 The submission noted that the OS comparison in MAVORIC was confounded by treatment switching in the vorinostat arm (73.1% of patients switched). The ESC noted that baseline characteristics of patients between the switchers and non-switchers appeared balanced for most categories with the exception of race where there were more Caucasian patients in the switching group (76.3% vs 62.7%) and CTCL subtype where there were more MF patients in the non-switching group (64.7% vs 48.9%). The ESC noted that reporting of the baseline characteristics of patients was incomplete as it did not include all of the baseline characteristics.³ In addition, the ESC noted that although the proposed PBS restriction includes patients receiving SCT these patient were excluded (8.1% in the mogamulizumab and 7.3% in the vorinostat groups respectively) from the treatment switching analysis. The pre-PBAC response argued that the exclusion of patients receiving SCT from the treatment switching analysis was conservative as SCT is a potentially curative intervention and there was differential uptake across treatment arms in MAVORIC which may not be reflected in the real world setting. The PBAC considered that as the requested listing population included patients receiving SCT it follows that they should be included in the treatment switching analysis.
- 6.26 The submission presented four approaches to adjust for the impact of treatment switching on the comparison of survival, namely censoring switching, the rank-preserving structural failure time (RPSFT) model, the inverse probability of censoring weighting (IPCW), and the two-stage method (TSEM). The ESC considered it was reasonable to apply an adjustment for treatment switching. However, the submission did not adequately justify the approaches it took to adjust for treatment switching, particularly in terms of model selection and the patient characteristics used to inform those models. In addition, the ESC noted that each of the methods are prone to error if key assumptions are not met.⁴
- 6.27 A key assumption for the RPSFT method is a common treatment effect for patients randomised to mogamulizumab and for patients who later switch to mogamulizumab. The ESC noted it is unknown if this holds although the PFS data (see paragraph 6.18) suggest it may not.
- 6.28 The ESC noted that both IPCW and TSEM approaches assume that the data for patient characteristics that are prognostic factors for mortality and that influence the probability of switching are available, and are included in the model to predict the probability of switching.⁵ The ESC noted the submission modelled switching as a

³ Unreported baseline characteristics that could have been informative for assessment of crossover were: gender, region, body weight, clinical stage, current site of disease, CCR4 expression status, LDH (U/L), type of prior therapy received, systemic therapies, prior radiotherapy.

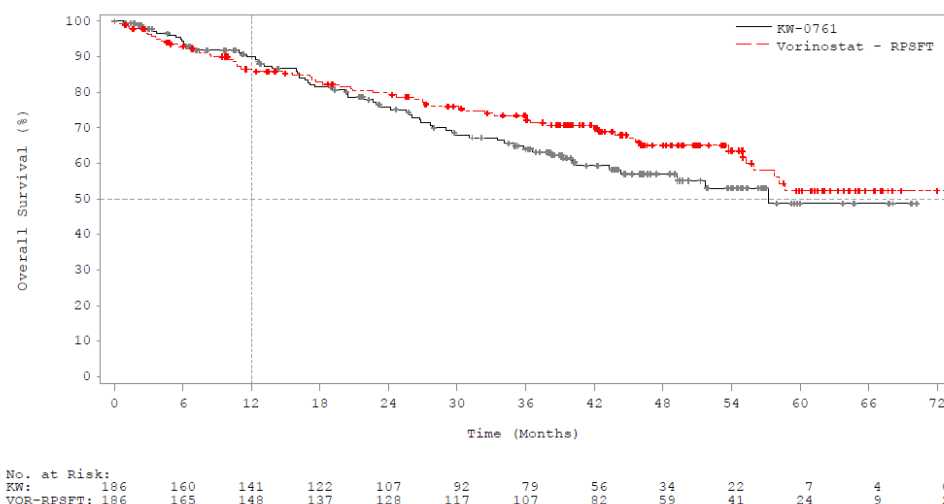
⁴ Latimer NR, et al. Treatment switching: statistical and decision-making challenges and approaches. *Int J Tech Assess Health Care* 2016;32:160-166

⁵ *ibid*

function of baseline characteristics including progression status, ECOG, histology (MF/SS), disease stage, age, adverse events, and region for IPCW. The same patient characteristics were used for TSEM to analyse the counterfactual for OS after progression. The submission reported that progression status, ECOG status, age and time⁶ are predictive of switching. However, the ESC considered it was unclear why the submission chose the remaining variables and excluded other baseline characteristics⁷ from the analysis.

6.29 The results of the adjustment for treatment switching are presented in Figure 4 (RPSFT), Figure 5 (IPCW, and TSEM) and Table 6. The submission presented a figure as the results for RPSFT but not an HR for the updated analysis. However, it is possible the HR for RPSFT would be above 1.00 given that the OS curve for vorinostat is above that for mogamulizumab (Figure 4). The ESC considered that this contradicts the RPSFT results from the December 2016 analysis (Table 6) where the HR was 0.74 (95% CI: 0.48, 1.14) and seems somewhat implausible given the intention of a crossover adjustment. The ESC considered that additional data from the sponsor on the HR for the 2nd March 2019 data cut-off for RPSFT adjusted OS would be informative. The pre-PBAC response reported that the HR for the preliminary RPSFT analysis in the overall ITT population was 1.26 (95% CI: 0.359, 4.423).

Figure 4: RPSFT adjusted Kaplan-Meier of overall survival (2nd March 2019 data cut-off)

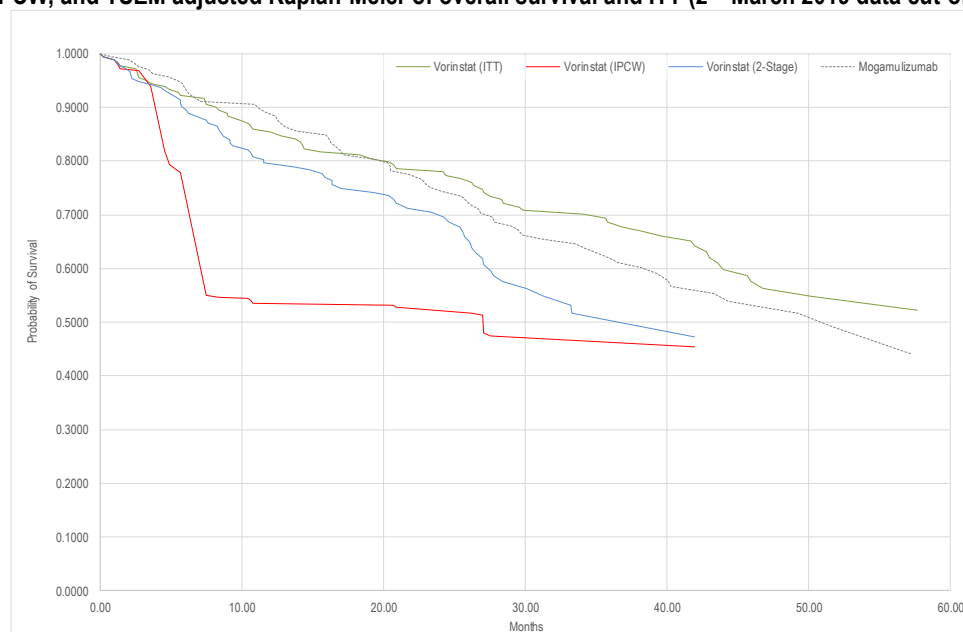


Source: Figure 2.35 p148 of the submission
Abbreviations: RPSFT = rank-preserving structural failure time

⁶ Restricted cubic splines are included to take account of time effects.

⁷ Other baseline characteristics include intolerance status, race, ethnicity, body weight, time from initial diagnosis, current sites of diseases, CCR4 expression status, LDH, and prior CTCL therapies.

Figure 5: IPCW, and TSEM adjusted Kaplan-Meier of overall survival and ITT (2nd March 2019 data cut-off)



Source: developed during the evaluation based on worksheet Section 3 Workbook of the submission.

Abbreviations: ITT = intention-to-treat; IPCW = inverse probability of censoring weighted; RPSFT = rank-preserving structural failure time

Table 6: Results from the adjustment for treatment switching

Analysis	HR	95% CI
March 2019 data cut-off		
IPCW	0.57	(0.26, 1.25)
TSEM	0.75	(0.53, 1.07)
RPSFT ^a	NR	NR
As randomised	1.13	(0.80, 1.60)
December 2016 data cut-off		
Censoring at crossover	0.71	(0.41, 1.24)
RPSFT	0.74	(0.48, 1.14)

Source: Table 2-70, p147; Table 2-40, p.119; Table 2-71, p149; Table 2-72, p151 of the submission.

Abbreviations: CI = confidence interval; HR = hazard ratio; IPCW = inverse probability of censoring weighted; RPSFT = rank-preserving structural failure time; TSEM = two-stage methods

Note: ^a No HR was reported in the 2nd March 2019 data cut-off while the results were presented in the KM curve (Figure 6).

- 6.30 While the point estimates for the HR for crossover adjusted OS varied across the adjustment methods, none were statistically significantly different from one but were numerically in favour of a survival advantage for mogamulizumab.
- 6.31 The largest difference was in the shape of the OS curve derived from the IPCW method which produced the OS outcome most favourable for mogamulizumab; HR=0.57, 95% CI: 0.26, 1.25. Application of the IPCW resulted in a substantial drop in the OS for vorinostat after around 5 months which might not be clinically plausible (Figure 5). The PSCR argued that the substantial drop in OS for vorinostat after around 5 months was a statistical artefact of the MAVORIC trial protocol, which allowed patients to crossover only after receiving two full cycles of treatment and an additional minimum 2 weeks waiting period. The PSCR stated that in routine clinical practice, the curve

would be smoother, and argued the economic model provides functionality to select one of several parametric survival distributions from baseline to reflect this if required. The ESC considered the drop in OS for vorinostat evident with IPCW was not clinically plausible.

- 6.32 The ESC noted there were only 16 non-switchers who were eligible for switching and they appeared to have more severe disease than the overall MAVORIC cohort (0% of the eligible non-switchers had ECOG = 0 vs approximately 57.0% of participants overall in the trial). As such the ESC considered the IPCW relied on a small group of patients who seemed to have worse health status than the overall study patients (IPCW places more weight on the OS of non-switchers who are eligible for switching). The ESC considered that in cases where there are very few control group patients who do not switch treatments the IPCW method becomes prone to error, because there is a higher likelihood that these remaining patients may not be representative of the wider trial population.⁸ The ESC considered that use of the IPCW as the preferred adjustment method in the submission, relative to the other methods, was not justified by the submission and favoured mogamulizumab.
- 6.33 The ESC acknowledged that TSEM was also prone to error if there are very few control group patients who do not switch, however the Committee considered TSEM was less sensitive to this issue than IPCW.⁹ The ESC noted that TSEM is reliant on switching occurring after a specific disease-related time-point, so that a secondary baseline can be defined. The ESC was satisfied that for the majority of patients (80.1%, 109/136) progressive disease was the specific disease-related time-point as it was the reason for switching. The ESC also noted that if there is a significant time-lag between the secondary baseline and the treatment switch TSEM can become prone to bias.¹⁰ Overall, the ESC considered the TSEM crossover approach would likely provide the most reliable method to adjust for treatment switching for the OS outcome in MAVORIC. However, the ESC considered additional data from the sponsor on the time between disease progression and commencing mogamulizumab for subjects randomised to vorinostat who crossed over would be informative. The pre-PBAC response stated that the time between vorinostat discontinuation and switch to mogamulizumab was very short (<5 days in 95% of switching patients and <10 days in all but one subject). However, the pre-PBAC response argued that the selection of analytical response would be more reasonably based on the plausibility of results than validation of individual underpinning assumptions and reiterated its claim that IPCW was the most reliable method to adjust for treatment switching.
- 6.34 A post-hoc analysis of time to next treatment (TTNT) was also conducted. The median TTNT was longer in the mogamulizumab arm (11.0 months; 95%CI 8.8, 12.6) than the

⁸ Latimer NR, et al. Treatment switching: statistical and decision-making challenges and approaches. *Int J Tech Assess Health Care* 2016;32:160-166

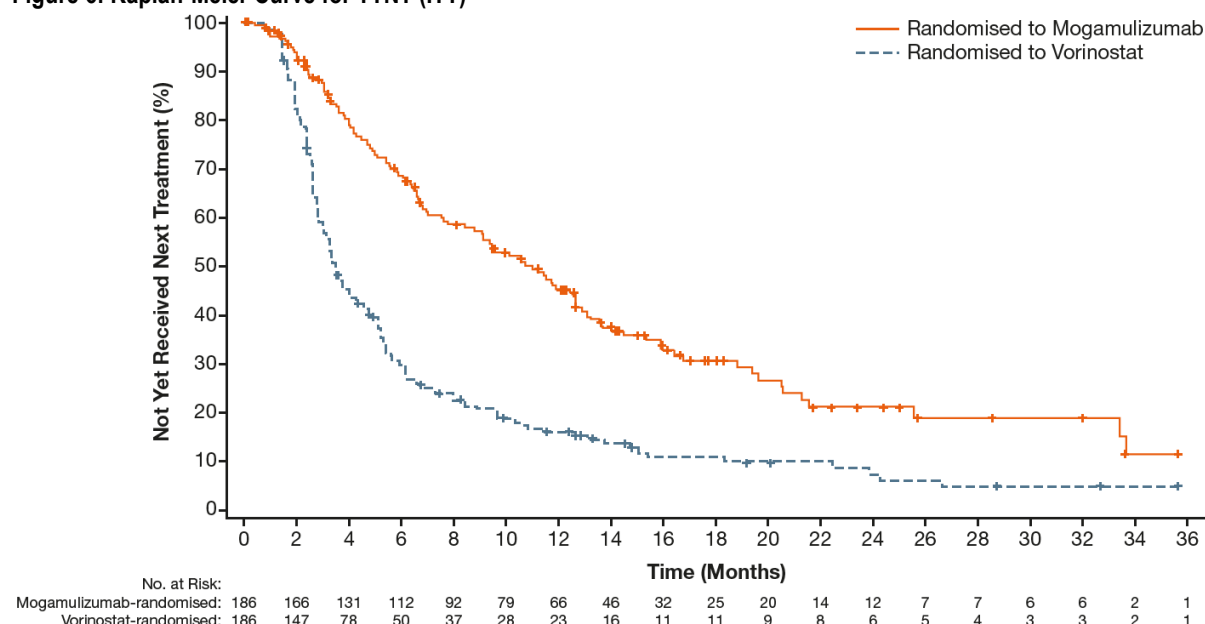
⁹ Ibid

¹⁰ Ibid

vorinostat arm (3.5 months; 95%CI 3.1, 4.3). A possible explanation is the one-way crossover design, where patients who progressed on vorinostat could commence mogamulizumab within 2 weeks of vorinostat. This would potentially bias the results against vorinostat as patients may cease vorinostat sooner than might otherwise occur in order to qualify for mogamulizumab therapy.

6.35 The KM plot for TTNT is shown in Figure 6.

Figure 6: Kaplan-Meier Curve for TTNT (ITT)



Source: Figure 2-19 (p122 of the submission)

Mogamulizumab vs brentuximab

6.36 At the time of data cut-off for ALCANZA the median follow-up was 22.9 months (95%CI 18.5, 26.1). Results of ORR4 in both the ITT and disease subgroups are presented in Table 7.

Table 7: Results of independent review facility assessed ORR4 in ALCANZA (ITT; MF and pcALCL subgroups)

Analysis group	n/N (%)		Risk difference (95% CI)	p-value
	Brentuximab	PC:MTX/BEX		
ITT (95% CI)	36/64 (56.3) (44.1, 68.4)	8/64 (12.5) (4.4, 20.6)	43.8 (29.1, 58.4)	<0.001
MF subgroup (95% CI)	24/48 (50.0) (35.9, 64.1)	5/49 (10.2) (3.4, 22.2)	39.8 (19.9, 56.2)	<0.001
pcALCL subgroup (95% CI)	12/16 (75.0) (47.6, 92.7)	3/15 (20.0) (4.3, 48.1)	55.0 (19.7, 80.4)	0.003

Source: Table 2-58 (p136 of the submission)

Abbreviations: CI = confidence interval; ITT= intent to treat; MF = mycosis fungoides; n = number of participants with event; N = total participants in group; pcALCL = primary cutaneous large cell lymphoma; PC:MTX/BEX = physician's choice of methotrexate or bexarotene. Bold indicates statistically significant difference.

6.37 Independent review facility (IRF) assessed ORR4 results favoured the brentuximab arm of the trial in both the ITT population (56.3% vs 12.5%) and in the CTCL subgroups

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(MF 50.0% vs 10.2%; pcALCL 75.0% vs 20.0%). The PSCR for brentuximab, highlighted that in ALCANZA the response to brentuximab was seen across a range of baseline CD30 expressions from 3% to 100% and there was no correlation between CD30 expression and ORR4 (paragraph 2.3, brentuximab PSD, July 2018 PBAC Meeting). The ORR4 results were consistent with the supportive analysis of the proportion of patients achieving an ORR (of any duration), which was also longer in the brentuximab group compared to PC:MTX/BEX (43 patients; 67% vs 13 patients; 20%; p <0.0001). The proportion of patients achieving a CR was also higher with brentuximab (10 patients; 16%) than with PC:MTX/BEX (1 patient; 2%; p = 0.0046).

- 6.38 The median IRF assessed PFS for brentuximab (16.7 months) was significantly longer than PC:MTX/BEX (3.5 months). A consistent difference in PFS was noted when stratified for MF and pcALCL subtypes. A summary of the PFS results for ALCANZA is presented in Table 8.

Table 8: Results of PFS in ALCANZA (ITT; MF and SS subgroups)

Analysis group	Brentuximab		PC:MTX/BEX		Difference in median	P-value	HR (95% CI)
	PFS (n, %)	Median (months)	PFS (n, %)	Median (months)			
ITT (95% CI)	36/64	16.7 (14.9, 22.8)	50/64	3.5 (2.4, 4.6)	13.2	< 0.001	0.27 (0.17, 0.43)
MF (95% CI)	30/48	15.9	41/49	3.5	12.4	NR	0.27 (0.164, 0.455)
pcALCL (95% CI)	6/16	27.5	9/15	5.3	22.2	NR	0.25 (0.081, 0.790)

Source: Table 2-61 (p137 of the submission); Table 7, Brentuximab, PSD, July 2018 PBAC Meeting.

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT= intent to treat; MF = mycosis fungoides; n = number of participants with event; N = total participants in group; NR = not reported; pcALCL = primary cutaneous large cell lymphoma; PC:MTX/BEX = physician's choice of methotrexate or bexarotene.

Bold indicates statistically significant result.

- 6.39 A naïve indirect comparison between MAVORIC and ALCANZA formed the basis of the clinical claim with the secondary comparator brentuximab. However, the clinical comparison of MAVORIC and ALCANZA was unreliable because of differences in the disease characteristics of the patients and the efficacy outcomes for the two trials. The PBAC previously considered that the difference in CTCL subtype and CD30 status between the patients in the two trials meant that the comparison was flawed and difficult to interpret (paragraph 7.7, brentuximab vedotin, PSD, July 2018 PBAC meeting). The results of the naïve comparison (see Table 9) were presented in the submission for completeness, and the submission acknowledged that few if any inferences could be drawn from them.

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Table 9: Naïve comparison of MAVORIC and ALCANZA outcomes

Outcome	MAVORIC		ALCANZA	
	Mogamulizumab	Vorinostat	Brentuximab	PC:MTX/BEX
ITT Population				
Median PFS – months				
Investigator	7.7	3.1	15.7	3.6
Independent	6.7	3.8	16.7	3.5
ORR – n/N (%)				
Investigator	52/186 (28.0)	9/186 (4.8)	NA	NA
Independent	43/186 (23.1)	7/186 (3.8)	43/64 (67.2)	13/64 (20.3)
Median DOR – months				
Investigator	14.1	9.1	NA	NA
Independent	16.1	NE	15.1	18.3
MF subgroup				
Median PFS – months				
Investigator	5.4	3.1	NA	NA
Independent	NA	NA	15.9	3.5
ORR – n/N (%)				
Investigator	22/105 (21.0)	7/99 (7.1)	NA	NA
Independent	NA	NA	31/48 (64.6)	8/49 (16.3)

Source: Table 2-73 (p153 of the Submission)

Abbreviations: DOR = duration of response; ITT = intent to treat; MF = mycosis fungoides; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported; PC:MTX/BEX = physician's choice of methotrexate or bexarotene; PFS = progression free survival

Comparative harms

Mogamulizumab vs vorinostat

6.40 A summary of adverse events (AEs) during the study in the safety analysis set (SAS) for MAVORIC is presented in Table 10.

Table 10: Summary of safety outcomes in MAVORIC (SAS)

n (%)	Pre-treatment and Randomised Treatment Period			Crossover Period
	Mogamulizumab (N = 184)	Vorinostat (N = 186)	RD (95% CI) ^c	Mogamulizumab (N = 136)
Adverse Events (AEs)				
Any AEs	180 (97.8)	185 (99.5)	-0.02 (-0.04, 0.01)	127 (93.4)
Any TEAEs	179 (97.3)	185 (99.5)	-0.02 (-0.05, 0.00)	127 (93.4)
Drug-related TEAEs	156 (84.8)	178 (95.7)	-0.11 (-0.17, -0.05)	99 (72.8)
Grade ≥ 3 AEs				
Any Grade ≥ 3 AEs	84 (45.7)	86 (46.2)	-0.01 (-0.11, 0.10)	48 (35.3)
Any Grade ≥ 3 TEAEs	78 (42.4)	85 (45.7)	-0.03 (-0.13, 0.07)	47 (34.6)
Drug-related Grade ≥ 3 TEAEs	47 (25.5)	65 (34.9)	-0.09 (-0.19, 0.00)	21 (15.4)
AEs with Outcome of Death	5 (2.7) ^b	9 (4.8) ^a	-0.02 (-0.06, 0.02)	4 (2.9) ^a
Serious Adverse Events (SAEs)				
Any SAEs	73 (39.7)	46 (24.7)	0.15 (0.06, 0.24)	38 (27.9)
Treatment-emergent SAEs	69 (37.5)	46 (24.7)	0.13 (0.03, 0.22)	36 (26.5)
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	0.03 (-0.04, 0.11)	14 (10.3)
Discontinuation due to AEs				
Any AEs	35 (19.0)	43 (23.1)	-0.04 (-0.12, 0.04)	30 (22.1)
Any TEAEs	35 (19.0)	43 (23.1)	-0.04 (-0.12, 0.04)	30 (22.1)
Drug-related TEAEs	25 (13.6)	40 (21.5)	-0.08 (-0.16, 0.00)	23 (16.9)

Source: Table 2-45 (p123 of the Submission).

Abbreviations: AE = adverse event; TEAE = treatment emergent adverse event; SAE = serious adverse event; n = number of participants with event; N = total participants in group; RD = risk difference

^a Includes one patient with TEAE with outcome of death that occurred during crossover and > 30 days after the last dose of vorinostat but was related to vorinostat.

^b Includes two patients with non TEAEs with outcome of death.

^c RD was calculated during the evaluation

Bold indicates statistically significant difference.

- 6.41 Drug-related AEs and drug-related Grade ≥ 3 AEs were slightly lower in the mogamulizumab arm compared to vorinostat (84.8% vs 95.7% for drug-related AEs, and 25.5% vs 34.9% for drug related Grade ≥ 3 AEs). The incidence of any serious adverse events (SAE) was higher in the mogamulizumab arm compared to vorinostat (39.7% vs 24.7%), and slightly higher for mogamulizumab in terms of drug-related SAEs (19.6% vs 16.1%). Discontinuation due to drug-related AEs was lower with the mogamulizumab arm compared to the vorinostat arm (13.6% vs 21.5).
- 6.42 The most common treatment-related TEAEs of any grade for mogamulizumab were infusion-related reactions, drug rash, diarrhoea and fatigue. The majority of these events were mild to moderate in severity; a Grade ≥ 3 infusion-related reaction occurred in 3 (1.6%) patients. For the vorinostat arm, the most common treatment-related TEAEs were diarrhoea, nausea, fatigue and thrombocytopenia.
- 6.43 In the crossover population, the incidence of AEs and Grade ≥ 3 AEs was lower than in either the mogamulizumab randomised patients or vorinostat treatment period. Drug related SAEs were lower in the crossover population (10.3%) compared to either the mogamulizumab randomised patients or vorinostat treatment period (19.6% vs 16.1%). However, discontinuation due to drug-related AEs was slightly higher in the

crossover population (16.9%) compared to the mogamulizumab randomised patients (13.6%) but lower than in the vorinostat treatment period (21.5%).

Mogamulizumab vs brentuximab

6.44 A summary of safety outcomes in the SAS for ALCANZA is presented in Table 11. At least one TEAE of any grade was reported in 95% of patients in the brentuximab arm and 90% in the PC:MTX/BEX arm. Grade ≥ 3 TEAEs were reported in 41% of patients in the brentuximab group and 47% of patients in the comparator group; drug-related Grade ≥ 3 AEs were the same in both arms.

Table 11: Summary of safety outcomes in ALCANZA (SAS)

n (%)	Brentuximab (n = 66)	PC:MTX/BEX (n = 62)	RD (95% CI) ^b	Total (N = 128)
Any AE	63 (95)	56 (90)	0.05 (-0.04, 0.14)	119 (93)
Any Grade ≥ 3 AE	27 (41)	29 (47)	-0.06 (-0.23, 0.11)	56 (44)
Drug-related AE	57 (86)	44 (71)	0.15 (0.01, 0.29)	101 (79)
Drug-related Grade ≥ 3 AE	19 (29)	18 (29)	0.00 (-0.16, 0.15)	37 (29)
SAE	19 (29)	18 (29)	0.00 (-0.16, 0.15)	37 (29)
Drug-related SAE	9 (14)	3 (5)	0.09 (-0.01, 0.19)	12 (9)
Discontinuation due to AE	16 (24)	5 (8)	0.16 (0.04, 0.29)	21 (16)
On-treatment deaths ^a	4 (6)	0	0.06 (0.00, 0.12)	4 (3)

Source: Table 2-66 (p143 of the Submission).

Abbreviations: AE = adverse event; n = number of participants with event; N = total participants in group; PC:MTX/BEX = physician's choice of methotrexate or bexarotene; SAE = serious adverse event.

^a On-treatment deaths are defined as deaths that occur within 30-days after the last dose of study drug.

^b RD was calculated during the evaluation

Bold indicates statistically significant difference.

Benefits/harms

Mogamulizumab vs vorinostat

6.45 A summary of the comparative benefits and harms for mogamulizumab versus vorinostat based on MAVORIC is presented in Table 12.

Table 12: Summary of comparative benefits and harms for mogamulizumab versus vorinostat

Benefits					
Progression free survival (median duration of follow-up 17.0 months)					
Event	Mogamulizumab	Vorinostat	Absolute Difference		HR (95% CI)
Progressed, n (%)	110/186 (59.1)	131/186 (70.4)			0.53 (0.41, 0.69)
Median PFS, months (95% CI)	7.7 (5.7, 10.3)	3.1 (2.9, 4.1)	4.6		P <0.0001
% not progressed at 6 months (95% CI) ^a	54.7 (46.6, 62.1)	35.1 (27.4, 42.9)	19.6 ^c		
% not progressed at 18 months (95% CI) ^a	27.9 (20.1, 36.3)	13.8 (7.0, 22.8)	14.1 ^c		
% not progressed at 30 months (95% CI) ^a	19.6 (11.5, 29.3)	10.3 (3.9, 20.4)	9.3 ^c		
Overall survival (median duration of follow-up 17.0 months) ^b					
Died, n (%)	40/186 (21.5)	47/186 (25.3)			0.93 (0.61, 1.43)
Median OS, months (95% CI)	NR (NR, NR)	43.9 (43.6, NR)	NE ^c		P = 0.94
Harms (median duration of follow-up 17.0 months)					
Potentially clinically relevant adverse events (any Grade)	Mogamulizumab (N = 184)	Vorinostat (N = 186)	Event rate/100 patients		RD ^c (95% CI)
			Mogamulizumab	Vorinostat	
Drug eruption	42	1	23	1	0.22 (0.16, 0.28)
Infusion related reactions	61	1	33	1	0.33 (0.26, 0.39)
Diarrhoea	19	103	10	55	-0.45 (-0.53, -0.37)
Nausea	17	71	9	38	-0.29 (-0.37, -0.21)
Dysgeusia	6	52	3	28	-0.25 (-0.32, -0.18)
Blood creatinine increased	1	45	1	24	-0.24 (-0.30, -0.17)
Thrombocytopenia	14	56	8	30	-0.22 (-0.30, -0.15)
Decreased appetite	5	40	3	22	-0.19 (-0.25, -0.12)

Source: Compiled during the evaluation. Table 2-28 (p109 of the Submission), Table 11.4.1-3 p130 MAVORIC CSR.

Abbreviations: CI = confidence interval; HR = hazard ratio; n = number of participants with event; N = total participants in group; OS = overall survival; PFS = progression free survival; RD = risk difference

^a Rate (%) of being alive without progression for at least the indicated months.

^b The OS results presented have not been adjusted for crossover. The median OS results are from the primary analysis (31st December 2016), as the updated analysis (2nd March 2019) presented in the submission (p147) only consisted of the KM analysis.

^c Calculated during the evaluation

Bold indicates statistically significant difference.

6.46 On the basis of the direct evidence presented by the submission from MAVORIC, for every 100 patients treated with mogamulizumab in comparison with vorinostat in patients with relapsed or refractory MF or SS CTCL after at least one prior therapy:

- Approximately 14 additional patients will be alive without progression for at least 18 months.
- Approximately 22 additional people will experience drug eruption (a drug related rash).
- Approximately 33 additional people will experience an infusion related reaction (including localised pain or rash).
- Approximately 45 fewer patients will experience diarrhoea.
- Approximately 29 fewer patients will experience nausea.
- Approximately 25 fewer patients will experience dysgeusia (an altered sense of taste).

- Approximately 24 fewer patients will experience an increase in blood creatinine level (laboratory test which can potentially indicate a change in kidney function).
- Approximately 22 fewer patients will experience thrombocytopenia (low platelet count).
- Approximately 19 fewer patients will experience decreased appetite.

Mogamulizumab vs brentuximab

6.47 The naïve indirect comparison between MAVORIC and ALCANZA presented in the submission did not allow for a quantitative comparison of the benefits and harms of mogamulizumab and brentuximab. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.48 For the primary clinical claim, the submission described mogamulizumab as superior in terms of effectiveness and comparable in terms of safety compared to vorinostat despite a longer duration of treatment.
- 6.49 During the evaluation the efficacy claim was considered adequately supported by the evidence from MAVORIC which demonstrated statistically significant gains in PFS and ORR for mogamulizumab compared to vorinostat. However, it was noted that a large proportion of patients in the vorinostat arm crossed over to mogamulizumab, and the impact of this on the PFS was unknown. Given that the assessment of PD included some outcome assessments that were subjective in nature, such as skin response measurement by investigator based on mSWAT, this may have influenced the determination of crossover eligibility. ESC previously noted that mSWAT performed by an unblinded investigator (as in MAVORIC) posed a potential risk of bias (paragraph 6.10, brentuximab, PSD, July 2018 PBAC Meeting). The PBAC agreed with the ESC that the level of crossover and the extent of censoring that occurred in MAVORIC could potentially impact PFS estimates. The PBAC also noted that the vorinostat ORR in the MAVORIC trial was substantially lower than reported in vorinostat studies previously considered by the PBAC (see paragraph 6.19).
- 6.50 A statistically significant difference in OS across the treatment groups was not demonstrated. Analyses adjusting for treatment switching showed a numerical difference in OS but no statistically significant difference (regardless of the adjustment method applied).
- 6.51 The PBAC considered the extent of benefit, if any, for mogamulizumab versus vorinostat could not be determined from the available evidence, and therefore did not consider the claim of superior comparative effectiveness to be adequately supported.
- 6.52 The PBAC considered that the claim of non-inferior comparative safety versus vorinostat was reasonable.

6.53 In terms of the secondary clinical claim, the submission described mogamulizumab as having a qualitatively (but unquantifiably) different mix of effectiveness and safety compared to brentuximab. The PBAC agreed with the ESC that it is difficult to draw any meaningful comparison from the evidence for mogamulizumab and brentuximab given that it was based on a naïve indirect comparison informed by two trials that contained patients with different baseline disease characteristics, including CTCL subtype and CD30 expression. Furthermore, there was no evidence presented in the submission regarding the use of mogamulizumab in CD30+ CTCL to inform the relevance of this comparison with brentuximab.

Economic analysis

6.54 The submission presented a cost-utility analysis (CUA) comparing mogamulizumab with vorinostat. An economic evaluation for mogamulizumab versus brentuximab was not provided. A summary of the model structure, key inputs and rationale for the model structure is presented in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Mogamulizumab vs vorinostat
Time horizon	20 years in the model base case (3 years median follow-up in MAVORIC)
Outcomes	Life years and quality adjusted life years (QALYs) gained
Methods used to generate results	Partitioned survival model
Health states	Disease control on treatment (DCOT) Surveillance without treatment Subsequent therapy Dead
Cycle length	7 days
Allocation to health states	Derived from time to event analyses (TOT, TTNT, and OS) of MAVORIC
Extrapolation method	Parametric model fitted to each treatment arm with gamma selected in base case for TOT, lognormal for TTNT and exponential for OS based on goodness of fit/external validation. No convergence applied. OS outcome for vorinostat was based on IPCW crossover adjusted (excluding patients who had an SCT). 59% of discounted QALYs (and 29% of discounted costs) occur in the extrapolated period.
Health related quality of life	MAVORIC-based; Utility values for DCOT = varied by cycles (0.695-0.813 for mogamulizumab and 0.592-0.763 for vorinostat); surveillance without treatment = 0.7675; subsequent therapy = 0.7185

Source: Table 3-1, p161 of the submission; developed during the evaluation

Abbreviations: DCOT = disease control on treatment; IPCW = inverse probability of censoring weighted; QALYs = Quality Adjusted Life Years gained; OS = overall survival; SCT= stem cell transplant; TOT = time on treatment; TTNT = time on next treatment

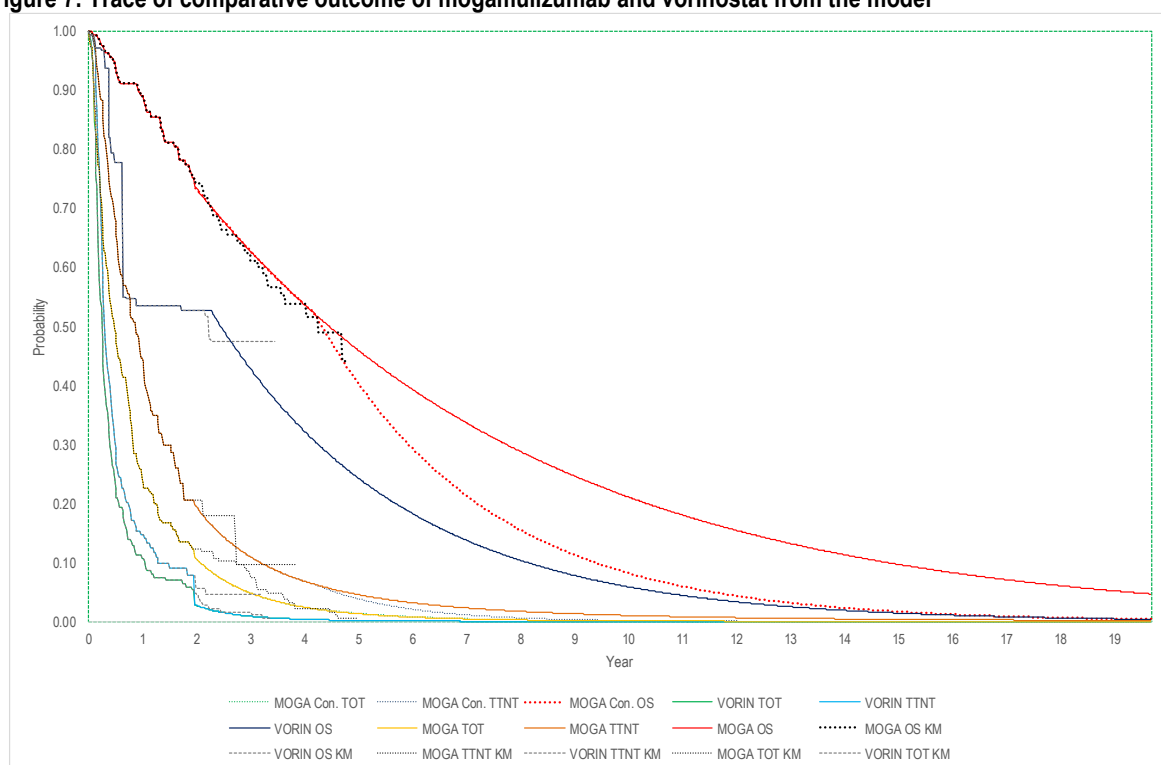
6.55 The model population was patients with refractory or relapsed CTCL which reflects the proposed PBS population. However, the data used in the model from MAVORIC were for MF and SS patients only. Patients who had an SCT were excluded from the analysis of OS used to inform the economic model.

6.56 During the evaluation the model time horizon of 20 years was considered long given the proposed PBS listing for mogamulizumab was for patients who have used at least one systemic therapy, and thus are likely to have a worse prognosis than de-novo

patients. In addition, patients in MAAVORIC, which are assumed to be the same as those in the economic model, had predominantly late stage disease; 62.4% with stage III or IV vs 37.6% IB or II disease. The PSCR stated that the results of the updated (March 2019) analysis of MAAVORIC indicate that around 50% of patients receiving mogamulizumab were still alive after 5-6 years. As such, the PSCR argued that a 20 year time horizon was appropriate. The PBAC noted the economic analyses for the vorinostat and brentuximab considerations for relapsed or refractory CTCL incorporated shorter time horizons and agreed with the evaluation that a more conservative time horizon may be appropriate for this patient population.

- 6.57 During the evaluation the approach used to estimate OS in the model was considered inadequately justified. Application of IPCW for crossover adjustment provided overly pessimistic and inadequately justified estimates of OS for vorinostat. During the period of the trial (3 years), based on the ITT analysis, there was a minimal difference in OS (mean of 0.30 months in favour of vorinostat). This increased to 7.9 months in favour of mogamulizumab based on the IPCW adjustment. The PSCR stated that this is a reasonable effect of extrapolating short term trial based outcomes to a lifetime horizon and adjusting these to exclude the confounding effect of crossover from vorinostat to mogamulizumab following disease progression. The ESC agreed with the evaluation that use of IPCW provided overly pessimistic and inadequately justified estimates of OS for vorinostat. As outlined in paragraph 6.33 the ESC considered the TSEM crossover approach would likely provide the most reliable method to adjust for treatment switching for the OS outcome in MAAVORIC.
- 6.58 None of the distributions used in the extrapolation of OS for mogamulizumab and vorinostat were validated with clinical evidence. The use of the exponential function for vorinostat was considered during the evaluation to be overly pessimistic, and it resulted in the lowest estimate of OS with a survival curve that dropped off rapidly. The ESC considered that the use of a Weibull function produced OS estimates for vorinostat that were higher than those from the exponential and an OS curve that appeared more realistic in shape.
- 6.59 The results of the traces from the comparative outcomes, including OS, predicted by the model are presented in Figure 7. Estimates noted as being “convergence” have been produced in Sensitivity Analyses as part of the evaluation. Overall, a high proportion of the OS results were obtained from the extrapolation period compared with the trial follow-up period (72% of the mogamulizumab and 61% of the vorinostat of the OS results were from the extrapolation period).

Figure 7: Trace of comparative outcome of mogamulizumab and vorinostat from the model



Source: Developed by the evaluators based on Section 3 Workbook.xlsx

Abbreviations: Con = convergence; KM = Kaplan-Meier; MOGA = mogamulizumab; VORIN = vorinostat; OS = overall survival; TOT = time on treatment; TTNT = time on treatment;

Note: convergence applied from median OS of mogamulizumab in MAVORIC by the Commentary in a sensitivity analysis

6.60 The submission included costs for post-progression treatments in the economic model, stating that it relied on the use of post-progression therapies in MAVORIC to determine the therapies included and the proportions of their use. However, the estimation of post-progression costs did not reflect the therapies used in MAVORIC. Post-progression therapy in the economic model was dominated by methotrexate; assumed to be used by 60% of patients in the model as compared with 4.3% of patients in MAVORIC. The assumed dominance of methotrexate as post progression therapy was not justified by the submission. Assigning a high proportion of use to methotrexate (60%) in the economic model resulted in low post-progression costs per cycle given that methotrexate is among the cheapest medicines assumed to be used as post-progression treatment. The PSCR argued that patterns of subsequent anti-cancer therapy will invariably be different between the trial and PBS settings, primarily because many of the therapies used in MAVORIC are not registered or reimbursed in Australia. The ESC considered that, when calculating costs for post-progression treatments in the economic model, a reduction in the proportion of use of methotrexate from 60% to 5% to reflect the use of such treatments in the MAVORIC trial would be appropriate.

6.61 In addition, patients in MAVORIC were treated with a range of therapies not included in the economic model (e.g. vorinostat, romidepsin, bexarotene, oral steroids, and

pralatrexate). The difference in the mix of post-progression therapies between the economic model and MAVORIC means that the model might not replicate the OS outcomes observed in MAVORIC. Moreover, the post-progression therapies included were not consistent with the proposed treatment algorithm which allows for the use of brentuximab. The post-progression costs were likely underestimated and favoured mogamulizumab given that the assumed duration of exposure to post-progression treatment was longer for mogamulizumab than vorinostat.

6.62 The submission reported utility values derived from MAVORIC. However, the precise methods applied to estimate the mean values provided nor the source for these values could be verified. From the information provided with the submission it was surmised that these values resulted from patient completion of the EQ-5D-3L in MAVORIC, to which UK tariffs were applied. Given the availability of Australian specific tariffs for this instrument, it would have been appropriate that they be applied for this submission. The ESC noted that the utility values from the re-analysis of EQ-5D-3L from MAVORIC for mogamulizumab and vorinostat were comparable with the total on-treatment period values reported as 0.773 (95% CI: 0.241, 1.305) and 0.762 (95% CI: 0.668, 0.856) respectively. Despite this the ESC noted the utilities applied for DCOT (or pre-progression on treatment) increased over time for mogamulizumab. The ESC considered it may be more appropriate to assume equal utilities in the DCOT health state. The pre-PBAC response stated that the increase in utilities in the mogamulizumab group over time was an observed outcome in the MAVORIC trial. The sponsor argued that the observation may be a true effect, reflecting the superior effectiveness and different safety profile of mogamulizumab, but also acknowledged that it could also be attributed to statistical factors, or chance.

6.63 A summary of the key drivers of the model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: \$55,000 to < \$75,000/QALY gained
Adjustment for crossover	IPCW provided overly pessimistic OS outcomes for vorinostat relative to other adjustment methods.	High, favoured mogamulizumab; using the TSEM increased the ICER to \$135,000 to < \$155,000 per QALY
Convergence	No convergence applied to extrapolation of outcomes resulting in an ongoing treatment effect for mogamulizumab.	High, favoured mogamulizumab; applying convergence from median OS of mogamulizumab in MAVORIC increased the ICER to \$95,000 to < \$115,000 per QALY
Extrapolation function for vorinostat	Exponential was overly conservative for vorinostat and may not adequately describe the data.	High, favoured mogamulizumab, using Weibull increased the ICER to \$75,000 to < \$95,000 per QALY

Source: developed during the evaluation using Section 3 worksheet

Abbreviations: ICER= incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighted; KM = Kaplan-Meier; QALYs = quality adjusted life years; OS = overall survival; TSEM = two-stage methods

6.64 The results from the economic evaluation are summarised in Table 15. These results were based on the published price of the subsequent therapy (except for brentuximab where the submission assumed a rebate of █% of the published price). The ICER/QALY was estimated at \$55,000 to < \$75,000.

Table 15: Results of the economic evaluation

	Mogamulizumab	Vorinostat	Increment
Costs	\$█	\$50,639	\$█
Life years	5.0270	2.8932	2.1338
QALYS	3.6793	2.0665	1.6128
Incremental cost per life year gained			\$█
Incremental cost per QALY gained			\$█

Source: Table 3.25, p.192 of the submission

Abbreviations: QALYs= quality adjusted life years

6.65 The results of key univariate and multivariate sensitivity analyses from the submission and prepared by the evaluation are summarised in Table 16.

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Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	%Change
Base case	\$ [REDACTED]	1.6128	\$ [REDACTED]	
Time horizon (base case 20-year)				
• 10-year	\$ [REDACTED]	1.2735	\$ [REDACTED]	+21%
• 15-year ^a	\$ [REDACTED]	1.5138	\$ [REDACTED]	+5%
OS extrapolation (base case exponential)^a				
• Weibull (vorinostat)	\$ [REDACTED]	1.1362	\$ [REDACTED]	+33%
• Gompertz (mogamulizumab)	\$ [REDACTED]	1.1727	\$ [REDACTED]	+30%
Convergence (base case no convergence)^a				
• From median follow-up (week 156)	\$ [REDACTED]	0.8253	\$ [REDACTED]	+79%
• From median OS mogamulizumab (week 223) ^b	\$ [REDACTED]	0.9893	\$ [REDACTED]	+51%
Adjustment of OS for treatment switching (base case IPCW)				
• TSEM	\$ [REDACTED]	0.7592	\$ [REDACTED]	+89%
• ITT (no crossover adjustment applied).	\$ [REDACTED]	-0.1760	Dominant	-
Post-progression costs (base case per the submission; methotrexate 60% of use)^a				
• Methotrexate 5% ^c	\$ [REDACTED]	1.6128	\$ [REDACTED]	+13%
Multivariate analyses				
• TSEM + 15-year time horizon ^a	\$ [REDACTED]	0.6963	\$ [REDACTED]	+105%
• TSEM + convergence median OS mogamulizumab ^a	\$ [REDACTED]	0.4429	\$ [REDACTED]	+212%
• Weibull for vorinostat OS, and Gompertz for mogamulizumab OS ^a	\$ [REDACTED]	0.6962	\$ [REDACTED]	+105%
• TSEM + Weibull for vorinostat OS ^d	\$ [REDACTED]	0.7732	\$ [REDACTED]	+86%
• TSEM + Weibull for vorinostat OS + increased post-progression costs (methotrexate 5% not 60%) ^d	\$ [REDACTED]	0.7732	\$ [REDACTED]	+90%
• TSEM + Weibull for vorinostat OS + increased post-progression costs (methotrexate 5%) + equal utilities in DCOT health state (mogamulizumab based) ^d	\$ [REDACTED]	0.7420	\$ [REDACTED]	+98%
• TSEM + Weibull for vorinostat OS + increased post-progression costs (methotrexate 5%) + equal utilities in DCOT health state (vorinostat based) ^d	\$ [REDACTED]	0.6855	\$ [REDACTED]	+114%

Source: developed using the economic excel model provided by the submission (the submission reported the ICER for 10-year time horizon, TSEM, and ITT (crossover) but did not report incremental costs and QALY and %change).

Abbreviations: DCOT = Disease control on treatment; ICER= incremental cost effectiveness ratio; IPCW = inverse probability of censoring weighted; ITT = intention-to-treat; KM = Kaplan-Meier; QALYs = Quality Adjusted Life Years gained; OS = overall survival; TOT = time on treatment; TSEM = two-stage methods; TTNT = time to next treatment

Note: ^a conducted during the evaluation, ^bused median OS of mogamulizumab was 51.7 months that was approximated to 223 weeks (median OS of vorinostat was 58.37 months), Table 2.70, p145 of the submission; ^c The 5% was used to reflect the use of methotrexate in MAVORIC (4.3%). The rest of methotrexate used in the model (55%) was arbitrarily redistributed to other five post-progression treatments (11% for each treatment), ^d Calculated during the preparation of the ESC Advice.

The redacted table shows ICERs in the range of \$55,000 to < \$75,000 per QALY, to \$155,000 to < \$255,000 per QALY.

6.66 Overall, the results were most sensitive to changes in the time horizon, method of adjusting for crossover, convergence of the extrapolation functions, the extrapolation function applied to OS for vorinostat and post-progression costs.

6.67 The ESC noted that multivariate analysis using TSEM to adjust for treatment switching, the Weibull function as the basis for extrapolation of OS for vorinostat, decreasing the use of methotrexate to 5% and equal utilities in DCOT health state (mogamulizumab based) increased the base case ICER by 98%.

Drug cost/patient/year \$ [REDACTED]

6.68 The average time on treatment estimated from the model was 45 weeks which translated into 24.89 infusions of mogamulizumab. This resulted in a drug cost/patient/year for mogamulizumab of \$ [REDACTED]. The cost per patient for mogamulizumab and vorinostat are summarised in Table 17.

Table 17: Drug cost per patient for mogamulizumab and vorinostat

	Mogamulizumab Trial dose and duration	Mogamulizumab Model	Mogamulizumab Financial estimates	Vorinostat Trial dose and duration	Vorinostat Model	Vorinostat Financial estimates
Mean dose intensity	94.41%	94.41%	95.00%	88.96%	88.91%	89.00%
Mean duration	19.10 infusions	24.89 infusions	24.80 infusions	20.60 weeks	24.15 weeks	4.80 30-day scripts
Cost	\$ [REDACTED] (per infusion)	\$ [REDACTED] (per infusion)	\$ [REDACTED] (per infusion)	\$1,039.32 (per week)	\$1,039.32 (per week)	\$4,454.24 (per 30-day script)
Cost/patient	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$19,046.33	\$22,316.03	\$19,028.51

Source: Table 12.1.1-1 p167-168 of the CSR; Section 3 workbook; Section 4 workbook;

Note: cost/patient/year = mean dose intensity x mean duration x cost/patient (per infusion or per week or per 30-day script)

Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC. The submission used an epidemiological approach, applying both Australian and international data to estimate the prevalence of the disease as outlined in Table 18. Applying an epidemiological approach may have been justified given that the submission sought a listing broader than that of vorinostat and brentuximab. However, the submission applied oversimplified assumptions regarding the eligible patient population, inputs that could not be verified with respect to patients' progression on prior therapies and did not adequately account for differences in the current PBS populations for vorinostat (SCT ineligible) and brentuximab (CD30+) that were likely to be different from the proposed mogamulizumab population. On balance, during the evaluation it was considered unclear whether the resulting utilisation estimates were under or over-estimated.

Table 18: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent population	Using reported 33-year prevalence of NHL reported by AIHW in 2014 (44,783 patients), the submission projected 51,442 patients with NHL in 2021 (assuming 2% growth of the Australian population; ABS). The submission assumed 3% of NHL was CTCL based on LRC 2019 and Huhes et al. 2016. This resulted in the estimated number patients with CTCL of 1,543 in 2021.	May be reasonable
Total patients	<ul style="list-style-type: none"> ○ 20% of patients have RR after ≥ 1 prior systemic therapy (assumption) ○ 50% of eligible patients elect further pharmacotherapy (assumption) 	Uncertain and unjustified in the submission.
Uptake rate	14% in Year 1 increasing to 40% in Year 4-6. Based on overseas experience and local market research	Appears reasonable based on the available data
Compliance rate	95% compliance rate based on MAVORIC	Reasonable
Dose/duration	24.8 scripts a year; 8 scripts for initial treatment; 24 scripts for continuing treatment (70% of initial patients based on MAVORIC)	Consistent with the dose/duration in the economic evaluation
Offsets for comparator/ subsequent therapies	50% of mogamulizumab use will be as a replacement for vorinostat and brentuximab (70% of replacement is for vorinostat and 30% for brentuximab)	Unjustified. Brentuximab was not included in the economic evaluation
MBS	None	Administration cost (\$99.50 per infusion) while included in the economic model, it was not included in the financial estimate.

Source: Developed for the Commentary during the evaluation.

Abbreviations: ABS = Australia Bureau of Statistics; AIHW = Australia Institute of Health and Welfare; CTCL = Cutaneous T-cell lymphoma; MBS = Medical Benefits Schedule; NHL = Non-Hodgkin's Lymphoma; PBS = Pharmaceutical Benefits Scheme; RR = relapsed or refractory.

- 6.70 The submission used the prevalence of Non-Hodgkin Lymphoma NHL (AIHW 2014) and assumed that 3% of patients had CTCL based on published literature (LCR 2019, and Hughes et al. 2016). The value of 3% could not be located in the literature referred to by the submission, but appears to be supported by Smith et al. 2015¹¹ who report that 3.5% of NHL cases had CTCL.
- 6.71 The submission assumed that 20% of the estimated prevalent CTCL patients would progress on prior systemic therapies, and further assumed that 50% of the progressed patients would elect further pharmacotherapy including the proposed and current PBS medicines for CTCL. These proportions were unverified. The proportion electing further pharmacotherapies may have been underestimated, given that 73.1% of vorinostat patients in MAVORIC (more heavily pre-treated patients than those likely to commence PBS eligible treatment) elected to commence mogamulizumab therapy as crossover patients.
- 6.72 The submission assumed that 50% of mogamulizumab will replace vorinostat and brentuximab. The submission further assumed that 70% of the replacement will be in

¹¹ Smith A, et.al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer* 2015;112: 1575-1584.

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place of vorinostat and 30% for brentuximab. The remaining 50% of the assumed mogamulizumab use was assumed to occur before or after vorinostat and brentuximab (displacement). This was unjustified and oversimplified given that the interchangeability across the medicines is limited:

- Not all of the proposed CTCL patients who progress on mogamulizumab will be eligible for vorinostat and brentuximab, as the use of vorinostat and brentuximab will be limited to patients who are SCT ineligible (vorinostat) and those who are CD30+ (brentuximab).
- All patients who progress on vorinostat and brentuximab will be eligible for mogamulizumab. However, these patients represent only part of the proposed CTCL patient population.

These differences were not well accounted for in the submission. However, it is acknowledged that quantifying such use would be complicated given an absence of information on the prevalence of patients eligible for CTCL medicines.

6.73 The expected vorinostat use was estimated based on data from MAVORIC (compliance and mean TOT). This might not reflect the current use of vorinostat given that PBS patients (who are SCT ineligible) might have poorer health than those in MAVORIC.

6.74 The estimated number of patients treated, scripts dispensed and financial implications of the proposed listing are summarised in Table 19. In forming these estimates, the submission has assumed that all patients commence on the first day of each year, allowing the maximum possible number of scripts for initiation and continuation to occur in each year. Adjusting for the timing of treatment commencement would be anticipated to reduce the script volume in year 1, with negligible effect thereafter.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed	█	█	█	█	█	█
Estimated financial implications of mogamulizumab						
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Estimated financial implications for vorinostat and brentuximab						
Cost to PBS/RPBS less copayments	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Net financial implications						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS/ Services Australia/other	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to PBS/RPBS/MBS/Services Australia ^a	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table 4-2, p199; Table 4-4, p200 of the submission

Abbreviations: MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

^a Update to the net cost is due to the addition of the impact on MBS services.

- 6.75 At Year 6 the estimated number of patients was < 500 and the net cost to the PBS/RPBS of listing mogamulizumab was estimated to be \$0 to < \$10 million, and a total of \$30 million to < \$40 million in the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

- 6.76 No risk-sharing arrangements (RSA) were proposed. The submission noted that the sponsor is in principle supportive of the development of an appropriate RSA as part of any PBS listing for mogamulizumab.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of mogamulizumab for the treatment of patients with relapsed or refractory cutaneous T cell lymphoma (CTCL). The PBAC considered that the extent of benefit for mogamulizumab in terms of progression free survival (PFS) and overall survival (OS) was uncertain. In addition, the PBAC considered the incremental cost-effectiveness ratio (ICER) was unacceptably high and uncertain at the proposed price, and the estimated financial impact was uncertain.
- 7.2 The PBAC welcomed the input from individuals, health care professionals and organisations which highlighted the need for new treatment options for patients with relapsed or refractory CTCL.
- 7.3 The PBAC accepted the nomination of vorinostat as the main comparator and brentuximab vedotin (hereafter referred to as brentuximab) as the secondary comparator.
- 7.4 The PBAC considered the key trial (MAVORIC) to have a high risk of bias due to the open label design and level of crossover. The PBAC noted the large proportion of patients in the vorinostat arm who crossed over to mogamulizumab (n = 136; 73.1%) based on investigator assessed disease progression (n = 109) or vorinostat intolerance (n=27). The PBAC considered the use of the potentially subjective modified Severity Weighted Assessment Tool (mSWAT) in the assessment of disease progression may have influenced the determination of crossover eligibility in this open label trial. The PBAC noted that independent review (IR) assessment of PFS also relied on the investigator assessment of mSWAT. In addition, the PBAC noted that the trial protocol allowed patients to crossover after receiving two full cycles of vorinostat and considered that the median number of cycles initiated for patients allocated to this arm (3.0 cycles) indicated that crossover occurred early.
- 7.5 The PBAC noted that a statistically significant difference in favour of mogamulizumab was reported for both investigator (HR = 0.53, 95% CI: 0.41, 0.69) and IR (HR = 0.64, 95% CI: 0.49, 0.84) assessed PFS. The PBAC noted a high number of patients in both arms were censored from the primary analysis for PFS (40.9% of mogamulizumab arm and 29.6% of vorinostat arm, see paragraph 6.17). The PBAC considered that due to the level of crossover and the extent of censoring that occurred in MAVORIC it was

uncertain as to whether the effects on PFS were predominantly the results from the individual treatments or the crossover design. The PBAC also noted that the median PFS was longer for the crossover population (8.9 months, 95% CI: 5.4, 14.8) than the observed PFS in either the mogamulizumab or vorinostat arms (7.7 months, 95% CI: 5.7, 10.3 vs 3.1 months; 95% CI: 2.9, 4.1) and considered that there was some indication that crossover patients may perform better.

- 7.6 The PBAC noted that none of the methods applied to adjust OS for treatment switching within the MAJORIC trial resulted in statistically significant hazard ratios for OS for mogamulizumab compared with vorinostat. The PBAC recalled that 73.1% of patients in the vorinostat arm crossed over to mogamulizumab and did so early in the trial (see paragraph 7.4). As such, the PBAC considered it unlikely that any of the methods applied to adjust OS for treatment switching could obtain valid estimates for the incremental benefit of mogamulizumab over vorinostat.
- 7.7 The PBAC considered the extent of benefit, if any, for mogamulizumab versus vorinostat could not be determined from the available evidence, and therefore did not consider the claim of superior comparative effectiveness to be adequately supported.
- 7.8 The PBAC noted that drug-related AEs and drug-related Grade ≥ 3 AEs were lower in the mogamulizumab arm compared to vorinostat. The PBAC also noted the incidence of any serious adverse events (SAE) and treatment-emergent SAEs was higher in the mogamulizumab arm compared to vorinostat (see paragraph 6.41). Overall, the PBAC considered that the claim of non-inferior comparative safety versus vorinostat was reasonable.
- 7.9 The PBAC noted the naïve comparison presented between mogamulizumab and brentuximab and reaffirmed its July 2018 advice that the comparison was uninformative on the basis that the trials presented – MAJORIC and ALCANZA – lacked a common treatment comparator and had different underlying populations (paragraph 7.7, brentuximab vedotin, PSD, July 2018 PBAC meeting).
- 7.10 The submission presented a cost-utility analysis comparing mogamulizumab with vorinostat. The PBAC noted the ICER was highly sensitive to changes in the time horizon, convergence of the extrapolation functions, the extrapolation function applied to OS for vorinostat and post-progression costs. Furthermore, the PBAC noted that estimation of OS in the model was based on the crossover adjusted inverse probability of censoring weighting (IPCW) approach. The PBAC also noted that use of the two-stage method (TSEM) to adjust for the impact of treatment switching on the comparison of survival in MAJORIC increased the base case ICER from \$55,000 to < \$75,000 per QALY to \$135,000 to < \$155,000 per QALY (see Table 16). For the reasons outlined paragraph 7.6, the PBAC considered it unlikely that any of the methods applied to adjust OS for treatment switching could obtain valid estimates. As such, the PBAC considered the ICER unacceptably high and uncertain and advised that

a cost-utility analysis may not be an appropriate method to determine the cost-effectiveness of mogamulizumab based on the data presented.

- 7.11 The PBAC noted the small number of patients eligible for treatment reflected the rarity of CTCL. The PBAC considered the estimates to be uncertain due to unjustified assumptions regarding the proportion of patients eligible for treatment and the displacement effect from mogamulizumab.
- 7.12 The PBAC acknowledged the rarity of CTCL and the difficulty of conducting phase 3 trials in this population but considered that the comparison did not provide good evidence of the extent of benefit of mogamulizumab over vorinostat. The PBAC advised that any resubmission would need to be a major submission with a revised economic evaluation which appropriately accounts for the uncertainty associated with the estimated incremental benefit. In addition, the PBAC considered it would be appropriate to exclude PBS subsidised access to mogamulizumab for CTCL subtypes such as LyP and pcALCL where $\geq 95\%$ of patients were alive at 5 years from a resubmission restriction.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

While disappointed with the outcome, Kyowa Kirin remains committed to working with the PBAC to provide access to mogamulizumab for Australians living with relapsed or refractory CTCL